M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DDLC-OTC DRUG STUDY BULLETIN NO. 40

DATE : DEC 15 1989

FROM : Chief
OTC Compliance Branch (HFD-312)
Division of Drug Labeling Compliance

SUBJECT: Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use; Final Monograph; Final Rule

TO : All Regional Food and Drug Directors
All District Directors
All Station Chiefs
Attn: OTC Field Contacts and
Compliance Branch Chiefs

PURPOSE

To notify the Districts that the OTC Final Monograph covering Nighttime Sleep-Aid drug products has published and to implement the compliance follow-up as described below. Two ingredients, diphenhydramine HCl and diphenhydramine citrate when used in conformance with 21 CFR 338 are considered safe and effective for use in OTC Nighttime Sleep-Aid Drug Products. Use of any other active ingredients in any such product introduced or delivered for introduction into interstate commerce on or after February 14, 1990 in the absence of an approved NDA will be in violation of the Federal Food, Drug, and Cosmetic Act.

SUMMARY

The final rule, in the form of a final monograph (FM), establishing conditions under which over-the-counter Nighttime Sleep-Aid drug products are generally recognized as safe and effective and not misbranded was published in the FEDERAL REGISTER, February 14, 1989, Vol. 54, No. 29, 54 FR 6814 (copy enclosed) and codified in 21 CFR Part 338. Any drug product marketed for use as an OTC Nighttime Sleep-Aid drug that is not in conformance with the monograph (21 CFR 338) will be considered a new drug within the meaning of section 201(p) of the FD&C Act (21 U.S.C. 321 (p)) for which an approved new drug application under section 505 of the act and 21 CFR 314 is required for marketing. In the absence of an approved new drug application, such a product is also misbranded under section 502 of the act.

Therefore, on or after February 14, 1990, any OTC drug product that is

LISTING OF MANUFACTURERS/DISTRIBUTORS/PRODUCTS SUBJECT TO THIS DRUG STUDY BULLETIN

DISTRICT	MARKETER	PRODUCT
BUF-DO	Approved Pharm Corp. Syracuse, NY	Sleep-Serene Tablets
CHI-DO	Walgreen Labs Chicago, IL	Sleep II
CIN-DO	Reese Chemical Cleveland, OH	Sleep-Ettes-D Tablets
DEN-DO	Nature's Way Products Inc. Springville, UT 84663	Naturest
DET-DO	Miles, Inc. Elkhart, IN	Nervine Capsules
	Health Care Industries, Inc. Elkhart, IN	Sleepocin Capsules
NSV-DO	Morton Pharmaceuticals Memphis, TN	Sedatabs Tablets
NWK-DO	Block Drug Co. Jersey City, NJ	Nytol Tablets
	Pioneer Pharm. Irvington, NJ	Diphenhydramine Capsules
NYK-DO	Randob Labs Ltd. P. O. Box 345 Mount Vernon, NY 10551	Dormin Capsules
	Whitehall Labs Div. American Home Products New York, New York	Sleep-Eze 3 Tablets
	Rugby Labs Rockville Centre, NY	Sleep Easy Tablets Sleepwell Capsules, Tablets
	Thompson Medical New York, NY	Sleepinol Capsules, Tablets, Caplets
PHI-DO	Beecham Products Pittsburgh, PA	Sominex Tablets Sominex Liquid
STL	Weeks & Leo Des Moines, IA	Sleep Cap

FDA
TALK PAPER
FOOD AND DRUG ADMINISTRATION
U.S. Department of Health, Education, and Welfare
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T79-21
May 1, 1979

Ed Nida
(301) 443-3285

METHAPYRILENE

An interim report from the National Cancer Institute indicating that methapyrilene causes liver cancer in experimental rats and mice was presented today for review by the Institute's advisory group, the Clearinghouse on Environmental Carcinogens. The Clearinghouse said the studies showed that methapyrilene is a potent carcinogen in animals and is a potential human carcinogen.

The report considered by the Clearinghouse today was initiated by FDA in October, 1977, after another study first raised the possibility that methapyrilene could cause cancer. FDA at that time asked NCI to expedite its testing of the drug.

Following the early reports of methapyrilene's carcinogenicity, manufacturers of nonprescription cough-cold drugs began removing it from their products. The ingredient remains in nonprescription nighttime sleep aids as well as some prescription drugs. In all nonprescription drugs, methapyrilene is listed in the ingredient statement on the label.

Following the NCI Clearinghouse meeting today, FDA issued the following statement:

The Clearinghouse today discussed a verbal presentation of data indicating that methapyrilene causes cancer.

FDA will ask NCI to expedite the transmittal to FDA of the actual study results. Once the data are received from NCI, FDA will evaluate them quickly.

-MORE-

The agency said last June that in the event the data produce evidence that "methapyrilene poses a health hazard as a carcinogen, the agency will take appropriate action to remove this active ingredient from the market, whatever its use, i.e., sleep aid, antihistamine."

If this action is taken, FDA will consider the need for a recall of methapyrilene-containing drugs and discuss with the manufacturers the possibility of reformulating their products.

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HEW NEWS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

P79-11
FOR IMMEDIATE RELEASE
June 8, 1979

(Food and Drug Administration)
PINES--(301) 443-3285
(Home)--(202) 363-4104

The following statement was issued today by Joseph A. Califano, Jr., Secretary of Health, Education and Welfare:

The over-the-counter drug manufacturers who have voluntarily agreed to recall products containing methapyrilene have acted in a responsible manner. The FDA has been concerned about the safety of this ingredient for some time and this concern was highlighted last month when studies evaluated by the National Cancer Institute Clearinghouse showed it to be a potent cancer-causing agent in laboratory animals.

This substance therefore poses a potential risk to humans, and people who take sleep aids or cough-cold or allergy remedies should discontinue using those containing methapyrilene. Consumers should consult the ingredient list on medicines in their possession to see whether methapyrilene appears.

FDA will carefully monitor the recall conducted by the firms to make certain that it is complete. The recall will not remove from retail shelves nasal sprays or skin medications containing methapyrilene, since the risk associated with those preparations is much lower.

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HEW NEWS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

P78-22
FOR IMMEDIATE RELEASE
June 12, 1978

(Food and Drug Administration)
Ed Nida - (301) 443-3285
(Home) - (301) 365-4574

As part of a continuing scientific review affecting several hundred thousand medicines now sold to Americans without prescription, the Food and Drug Administration today proposed new standards for permissable ingredients and labeling for night-time sleep aids and stimulant drugs.

The Agency further proposed to end the marketing of all nonprescription drugs now sold as daytime sedatives. This latter action is based on an FDA decision that the daytime sedatives now available provide no sedation but merely make people drowsy when they may not want to be -- i.e., while driving an automobile or operating machinery.

FDA also proposes that methapyrilene, an antihistimine, be excluded from the night-time sleep aids pending further study. Preliminary reports indicate the ingredient may cause tumors in test animals. FDA has asked the National Cancer Institute to expedite testing of the substance.

Today's proposal is FDA's second step in establishing new standards to assure the safety and effectiveness of night-time sleep aids, daytime sedatives and stimulants sold over the counter (OTC). The first step was publication some months ago of a report by a panel of nongovernment experts which reviewed for the Agency all ingredients used in these products. Today's proposal represents FDA's evaluation of the Panel report and all other available data.

-MORE-

FDA will accept written objections and requests for hearings for 60 days on the proposed standards. FDA will issue final standards at a later time.

When the standards are issued, any product labeled as a nonprescription daytime sedative would have to be removed from the market within six months, and any product labeled as a nonprescription night-time sleep aid or stimulant would have to comply with the formulation and labeling requirements of the standards. Products would be allowed to deviate from the standard only with specific FDA approval.

FDA finds that no ingredients now being used in nonprescription sleep aids meet the minimum legal requirements for safety and effectiveness, and proposes to allow one ingredient, pyrilamine, to stay on the market while further studies are being carried out.

FDA also proposes that sleep aids that remain on the market be labeled as follows: "helps fall asleep," "for relief of occasional sleeplessness," or "helps to reduce difficulty in falling asleep." The standard would require a warning statement to caution against using such drugs with alcohol.

The Agency finds caffeine to be the only safe and effective ingredient in nonprescription stimulants. The proposed label for such products would say: "helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness." Under FDA's proposal, the label would warn that exceeding the recommended dose may lead to increased nervousness, anxiety, irritability, difficulty in falling asleep or disturbances in heart rate and rhythm (palpitations).

-MORE-

The label would point out that the product contains about as much caffeine as a cup of coffee and should be taken cautiously with coffee, tea or cola drinks since they also contain caffeine.

Objections and requests for hearings may be submitted to the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Maryland 20857.

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HEW NEWS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

P79-14
FOR IMMEDIATE RELEASE
June 22, 1979

(Food and Drug Administration)
ED NIDA--(301) 443-3285
(Home)--(301) 365-4574

The Food and Drug Administration today announced its final decision to prohibit the sale of any nonprescription drug labeled as a daytime sedative.

FDA had announced last year its intention to do this. Since then many manufacturers have relabeled their products to market them as nighttime sleep aids, or have removed their products from the market.

Nonprescription daytime sedatives as well as nighttime sleep aids generally contain antihistamines, which make people drowsy.

FDA opposes the marketing of nonprescription drugs as daytime sedatives because there is no evidence that drowsiness helps relieve anxiety, and drowsiness is not a desirable side effect during the day, when people need to be alert. FDA has not opposed the sale of antihistamines as nighttime sleep aids since drowsiness can help people fall asleep.

A few daytime sedatives contain scopolamine or bromide, ingredients that FDA regards as being unsafe or ineffective for daytime sedative use.

The decision takes effect in six months. Any nonprescription drug labeled as a daytime sedative that is introduced in interstate commerce after that will be subject to FDA regulatory action.

Notice of the FDA order appears in the FEDERAL REGISTER June 22, 1979.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

JUN 15 1973

METHAPYRILENE - Form Letter to Marketers

Gentlemen:

This letter concerns the above referenced product(s) and any other methapyrilene-containing products for systemic or topical use, which now or have been manufactured, relabeled, repacked or distributed by your firm. All strengths and all lots are included.

A number of manufacturers of human drug products containing methapyrilene have voluntarily agreed to recall their products from the market. This decision was based on conclusions reached by the Food and Drug Administration after reviewing reports received from the National Cancer Institute that methapyrilene is a potent carcinogen in rats and is, therefore, a potential carcinogen in man. Your firm may be one of those taking this voluntary action. For your information, we are enclosing a copy of a public statement issued by the Food and Drug Administration regarding its conclusion that methapyrilene is a carcinogen.

In view of this new information, all human drugs containing methapyrilene for systemic or topical use are regarded as new drugs within the meaning of Section 201(p) of the Act. Therefore, all drugs for systemic or topical use containing methapyrilene are subject to regulatory action under Sections 502 and 505 of the Act.

Because of the potential hazard, the Food and Drug Administration is requesting of all firms that any manufacturing, relabeling, repackaging and/or distributing of human drug products containing methapyrilene for systemic or topical use be discontinued. Further, it is in the public interest that prompt recall be undertaken of all stocks of these products as follows:

1) Systemic products to the retail/dispensing level.

2) Topical products, nasal sprays and/or eardrops to the wholesale level.

These recalls will be classified by FDA as firm-initiated Class II. To determine the effectiveness of these recalls, checks should be made of at least ten (10) percent of the total number of your consignees. This is regarded as Level C in the FDA's Recall Guidelines (21 CFR 7.1 et. seq.) which were published in the June 16, 1978, Federal Register (43 F.R. 26202 et. seq.).

Our _____ District office will contact you promptly on this matter.

Sincerely yours,

Joseph P. Hile
Associate Commissioner for
Regulatory Affairs

Enclosure:
Public Statement Re Carcinogenicity
of Methapyrilene
Methapyrilene - List of Marketers

cc:
All RFDD's
All District Directors
All District Compliance Branches
HF-1
HF-2
HFC-1
HFC-2
HFW-1
HFY-1
HFD-1
HFD-2
HFD-4 (Morrison)
GCF-1 (Pfeiffer/Scarlet)
HFO-1
HFC-13
HFI-40
HFI-45

HFC-30
HFD-100 (Finkel)
HFD-102 (D'Aguanno)
HFD-300 (Byers)
cc (continued):
HFD-302 (2) (Koustenis)
HFD-310 (Apodaca)
HFD-312 (AJAronson)
HFD-300 R/F
DDLC File
OCPP File
HFA-224
AJAronson:jag:5/16/79 (1st R/D)
R/D Init: EPfeiffer:5/29/79 RHeller:5/23/79 GKoustenis:5/24/79
JHalperin:5/29/79 RApodaca:5/30/79
R/D Revised:AJAronson:jag:6/6/79
TMChin Init: Pending O.K. as to level of recall by Commissioner to Sec. HEW - 6/7/79
JPHile: Concurred, based on confirmation of level of recall for all products by Commissioner - 6/7/79
R/D Revised:AJAronson:jag:6/11/79
R/D Init: RApodaca:6/11/79 GKoustenis:6/11/79 AJAronson:6/11/79
TMChin:6/11/79 GDykstra:6/11/79
R/D Revised:AJAronson:jag:6/11/79
R/D Init: AJAronson:6/11/79 RApodaca:6/11/79 RHeller:6/11/79
TEByers:6/12/79
R/D Revised:AJAronson:jag:6/11/79
R/D Init: AJAronson:6/11/79 RApodaca:6/11/79 RHeller:6/11/79
GKoustenis:6/12/79 TEByers:6/12/79 JMorrison:6/12/79
JRCrout:6/12/79 JPHile:6/12/79
FINAL:6/15/79

Federal Register

Tuesday
February 14, 1989

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 338

Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use; Final Monograph; Final Rule

the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace, that could not only result in economic loss but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is providing an effective date of 12 months after the date of publication of the final monograph in the Federal Register.

In response to the proposed rule on OTC nighttime sleep-aid drug products, four consumers, two consumer groups, six drug manufacturers, one drug manufacturer association, and one consultant representing four different drug manufacturers submitted comments. Requests for oral hearing before the Commissioner were also received on 12 different issues. Copies of the comments and the hearing requests received are on public display in the Dockets Management Branch. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

In proceeding with this final monograph, the agency has considered all objections, requests for oral hearings, and the changes in the procedural regulations. In light of the changes in the OTC drug review procedural regulations and the withdrawal of methapyrilene from the marketplace (see below), many of the objections filed in response to the agency's proposed regulation on OTC nighttime sleep-aid drug products are no longer applicable, e.g., comments on testing guidelines and on methapyrilene. In those cases where the agency has agreed with submitted objections and has revised the final monograph accordingly, the Commissioner concludes that any requests for hearing are moot. Therefore, such hearing requests are not discussed in the following responses to comments.

One comment requested hearings on several aspects of the rule if the Commissioner, in making his decisions, relied upon evidence that was not in the public domain. The Commissioner advises that the agency's decisions in this rulemaking have been based entirely on the administrative record, which is publicly available in the Dockets Management Branch. Therefore, the Commissioner concludes that the comment is no longer requesting hearings on those issues. All other requests for hearing are discussed below.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the Federal Register of August 9, 1972 (37 FR 16029), or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments on OTC Nighttime Sleep-Aid Drug Products

1. One comment requested that the agency not remove nighttime sleep-aid drug products from the OTC market.

The tentative final monograph on nighttime sleep-aid drug products (43 FR 25544) did not propose to remove this entire class of drug products from the OTC market. The agency recognized the usefulness of this class of drugs, but concluded that the data available at that time were not sufficient for FDA to determine that any specific ingredients in this class of drugs were generally recognized as safe and effective. Since that time, additional data have been submitted to the OTC drug review to support the safety and effectiveness of diphenhydramine hydrochloride and diphenhydramine monocitrate (now named diphenhydramine citrate), and these ingredients are included in the final monograph for OTC nighttime sleep-aid drug products. In addition, products containing doxylamine succinate are marketed OTC as a nighttime sleep-aid under approved new drug applications (NDA's).

2. One comment argued that the Commissioner had failed to follow the prescribed procedures in issuing the tentative final monograph on OTC nighttime sleep-aids and that it is without legal authority. The comment also contended that the tentative final monograph is arbitrary, capricious, and not supported by substantial evidence and requested a hearing on this issue.

At the time of publication of the panel's report and recommended monograph in the Federal Register of December 8, 1975 (40 FR 57292), § 330.10(a)(6) provided for a comment period of 60 days after publication of a panel's report and recommended monograph, and a period of 30 days from the last day of the comment period for reply comments to be filed. In the report, the agency allowed for a comment period of 90 days, which conforms with current 330.10(a)(6). Section 330.10(a)(7) provided that after reviewing all comments and reply comments, a tentative final monograph would be published in the Federal Register. The agency received comments and reviewed them. In the Federal Register of June 13, 1978 (40 FR 57292), the agency responded to the comments in the tentative final monograph. Section 330.10(a)(7) has been subsequently expanded to require review of new data prior to publication of a tentative final monograph.

The comment does not specify what procedures it alleges that the Commissioner failed to follow and the agency is not aware of any. Therefore, the agency concludes that it followed the prescribed procedures set forth in 21 CFR 330.10(a)(6) and (7) for publishing a tentative final monograph on OTC nighttime sleep-aid drug products. The agency rejects the comment's contention that the tentative final monograph is without legal authority. The legal authority for this rulemaking process is provided by the Federal Food, Drug, and Cosmetic Act (the act), as cited in the "Authority" paragraph which immediately precedes the monograph. The agency's conclusions reached in the tentative final monograph are supported and well documented with references publicly available in the administrative record for this rulemaking. Therefore, the agency concludes the comment's contention is not valid. The Commissioner also concludes that a hearing on this issue is not warranted.

3. One comment objected to the statement in the tentative final monograph "that OTC drugs should contain only such inactive ingredients as are known to be safe and are necessary for pharmaceutical formulation" (43 FR 25544 at 25590). The comment contended that this statement is without sanction of law and is inconsistent with other FDA regulations. The comment requested revocation of the statement.

The statement in question was part of the preamble and not part of the tentative final monograph; thus, it need

undertake such studies for the public good.

The agency appreciates the comment's concerns. However, FDA's primary charge is to ensure that drugs in the marketplace are both safe and effective for their intended use, not to conduct original research in the development of new drugs. In addition, this final monograph contains ingredients that are considered safe and effective for use as OTC nighttime sleep-aids.

7. One comment urged the agency to recognize the legal status of the monographs issued under the OTC drug review as being interpretative rather than substantive regulations.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drugs published in the Federal Register of May 11, 1972 (37 FR 9464), and in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products published in the Federal Register of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

8. One comment disagreed with the agency's statement in the tentative final monograph that the Panel had gone beyond its charter in making statements on advertising (43 FR 25544 at 25545). The comment believed that the agency's statement was in contradiction to a later statement that the OTC advisory review panels "are free to comment, on any scientific or policy issue that they have considered in the course of their review" (43 FR 25558). The comment urged the agency to adopt a formal statement of policy with respect to advertising and include it in the monograph.

The agency disagrees with the comment that the two statements are in contradiction. The OTC advisory review panels were charged to advise the agency on the safety, effectiveness, and labeling of OTC drug products. They were not charged with making recommendations on advertising because the Federal Trade Commission (FTC), not FDA, is the agency that has the primary responsibility for regulating OTC drug advertising. FDA has the authority to regulate OTC drug advertising that constitutes labeling under the Federal Food, Drug, and Cosmetic Act. See, e.g., *United States* v. *Article of Drug * * * B-Complex Cholinos Capsules*, 362 F.2d 923 (3d Cir. 1966); *V.E. Irons, Inc.* v. *United States*, 244 F.2d 34 (10th Cir.); *cert. denied*, 354 U.S. 923 (1957). In addition, for an OTC drug to be generally recognized as safe and effective and not misbranded, the advertising for the drug must satisfy the FDA regulations in § 330.1(d) (21 CFR 330.1(d)), which state that the advertising may prescribe, recommend, or suggest the drug's use only under the conditions stated in the labeling. If advertising for an OTC nighttime sleep-aid drug product offers the product for conditions not included in the final monograph labeling, the drug product may be subject to regulatory action by FDA. Therefore, as stated in the tentative final monograph, advisory review panels are free to comment on any aspect of OTC drug regulation notwithstanding FDA's limited authority to implement their recommendations. Because the agency's jurisdiction over OTC drug advertising is already stated in the act and in existing agency regulations that are applicable to all OTC drug monographs, the comment's request for inclusion of a policy statement on advertising in this particular monograph is not necessary.

9. One comment disagreed with the agency's statements in the tentative final monograph that the Consumer Product Safety Commission (CPSC) and not FDA has the authority to place limitations on package size (43 FR 25544 at 25546). The comment stated that CPSC has authority to require child-resistant closures, but does not have the authority to regulate the quantity available in a product container. The comment expressed the belief that, under the act, FDA has authority to limit the conditions under which a drug is used including the quantity of drug in a container. Because of the Panel's concern for potential harm to children if large quantities of any nighttime sleep-aid are ingested, the comment requested that the agency restrict the quantity of a nighttime sleep-aid packaged per container to a safe level or incinde a warning that ingestion of large quantities could be lethal. The comment also requested a hearing on this issue.

The agency agrees with the comment that FDA does have authority to place limitations on package size when deemed necessary, e.g., the recommended limitations in the quantity of 1¼ grain (pediatric) aspirin tablets to 36 tablets per container (21 CFR 201.314(c)). Concerning the comment's request that the agency restrict the amount of drug in a nighttime sleep-aid container, however, no evidence has been presented to warrant such a restriction.

CPSC has the authority to require child-resistant closures. FDA is aware that CPSC has reviewed the available data on antihistamines and has determined that child-resistant closures are warranted for OTC drug products, including nighttime sleep-aids, containing more than 66 milligrams (mg) diphenhydramine base in any oral dosage form. (See 16 CFR 1700.14(a)(17).) The comment did not submit any data that indicate a need to limit the package size of OTC nighttime sleep-aid drug products containing diphenhydramine nor did it submit any data that indicate a need to include a warning that ingestion of large quantities could be lethal. Therefore, FDA does not believe that limiting the package size for OTC diphenhydramine-containing nighttime sleep-aids or a warning is necessary at this time. If the agency proposed limiting the package size of such drug products to 66 mg diphenhydramine or less, each package would contain only one adult dose of 50 mg. Limiting the package size to a single dose would be impractical. In view of CPSC's final rule on child-resistant packaging, the impracticality of limiting a package size to a single dose, and the comment's failure to submit data supporting the need for further action, the Commissioner concludes that a hearing by FDA on this issue is not warranted at this time.

10. One comment requested FDA to join with FTC in conducting hearings on the possibilities of deception in labeling and advertising caused by "look-alike/sound-alike" drugs. The comment noted that the agency's response to this issue was that if "look-alike/sound-alike" drugs presented an opportunity for abuse, appropriate action would be initiated under section 502(a) of the act (see comment 19, 43 FR 25544 at 25547). The comment maintained "that enough evidence is present to warrant affirmative action on this issue."

The agency recognizes the potential for deception in the marketing of OTC "look-alike/sound-alike" drugs, including certain OTC nighttime sleep-aids that bear a strong physical resemblance to certain controlled prescription drugs, or have trade names that sound like those of controlled drugs. Since publication of the tentative final monograph, the agency has become aware that there is widespread manufacturing, promotion, and marketing of these OTC "look-alikes." The agency has initiated actions, both under the counterfeit drug sections of the act (sections 201(g)(2) and 301(i)(2)) and separate from the OTC drug review, to

final monograph, but urged that this claim and the "sound sleep" claim both be included in the monograph. The comment also requested a hearing on this issue.

Another comment objected to the agency's Category II placement of the claim "helps you relax so you can fall asleep." Arguing that the agency conceded that nighttime sleep-aids provide a relaxant action, the comment referred to the agency's statement at 43 FR 25553 that such a "product will make one drowsy, not just relaxed * * *." The comment requested that this claim be moved from Category II to Category I.

The above classifications were made in the tentative final monograph before the agency received the results of any clinical studies that supported monograph status for any OTC nighttime sleep-aid drug. Since that time, the agency has evaluated the results of clinical studies that support the safety and effectiveness of diphenhydramine hydrochloride and diphenhydramine citrate for nighttime sleep-aid use. (See comment 22 below.)

In those studies, a number of efficacy variables related to the claims and terms requested by the comments were evaluated. These included the following: (1) How much did the medication help?, (2) wake time, (3) how rested when awoke?, (4) how sleepy during day?, (5) how energetic during day?, (6) sleep latency, (7) number of awakenings, (8) sleep duration, (9) depth of sleep, and (10) how good was the sleep?

As discussed in comment 22 below, in one study, diphenhydramine hydrochloride was significantly better ($p = .05$) than placebo for sleep latency, degree to which medication helped, depth of sleep, and quality (goodness) of sleep. At the less conservative .10 level of significance, diphenhydramine was better than placebo for the amount of time spent awake in bed. In another study, diphenhydramine was significantly better ($p = .05$) than placebo for sleep latency, degree to which medication helped, depth of sleep, quality (goodness) of sleep, feeling rested upon awakening, and degree of energy during previous day. At the less conservative .10 level of significance, diphenhydramine was better than placebo for the amount of time spent awake in bed. All other variables evaluated in the studies were not significant.

The claim relating to fewer awakenings, which was placed in Category III in the tentative final monograph, reads as follows: "Reduces the number of awakenings in persons who wake frequently during the night" (43 FR 25544 at 25588). The agency concluded that this would be a valid claim for OTC nighttime sleep-aids if supported by evidence in well-controlled studies. However, none of the studies submitted to support the effectiveness of diphenhydramine as an OTC nighttime sleep-aid supports that claim. Therefore, the scientific data are inadequate to allow inclusion of the "fewer awakenings" claim in the monograph.

Based on the results of the diphenhydramine studies, which showed that the nighttime sleep-aid drug improved depth of sleep, quality (goodness) of sleep, feeling rested upon awakening, and degree of energy during previous day, the agency concludes that the data support the terms "sound sleep," "restful sleep," "good night's sleep," and "refreshing sleep" for nighttime sleep-aid drug products. Further, the agency notes that the concept of rest is included in at least two dictionary definitions for "relax" (Refs. 1 and 2); therefore, the term "relaxing" sleep is also acceptable. However, the agency considers these terms to be descriptive statements that do not relate in a significant way to the safe and effective use of nighttime sleep-aid drug products and, therefore, does not consider such information to be necessary as part of the required indications for these products. Because these terms are examples of truthful and nonmisleading language, the agency would allow the terms to be included in labeling provided they are not intermixed with labeling established by the monograph. Based on the above discussion, the Commissioner concludes that a hearing on this issue is not warranted.

Regarding the statement (made by the agency in the tentative final monograph at 43 FR 25544 at 25553) referred to by the comment, the agency was not conceding that OTC nighttime sleep-aids act by relaxing, but rather intended to emphasize that these drugs act by making one drowsy. Regarding the claim "helps you relax so you can fall asleep," the agency considers such a claim as relating to the mechanism of action of the drug. This efficacy variable was not evaluated as part of the diphenhydramine studies. Therefore, because the data are inadequate to support such a claim, it is not being included in the monograph.

References

(1) "Webster's Collegiate Dictionary," G. and C. Merriam Co., Springfield, MA, 1978, s.v. "relaxing."

(2) "The American Heritage Dictionary of the English Language," Houghton Mifflin Co., Boston, 1976, s.v. "relaxing."

14. One comment objected to the warning in proposed § 338.50(c)(2): "If condition persists continuously for more than 2 weeks, consult your physician. Insomnia may be a symptom of serious underlying medical illness." The comment referred to reasoning provided in its earlier comment to the Panel's report that there is insufficient evidence of abuse of OTC nighttime sleep-aid drug products to warrant such a warning.

In addressing this issue in comment 51 of the tentative final monograph (43 FR 25544 at 25554), the agency tentatively concluded that the warning was necessary because it would help the user to determine when the limits of self-treatment have been reached. The present comment offers no basis to alter the agency's conclusions; therefore, the warning is included in the final monograph.

15. Several comments objected to the glaucoma warning proposed in § 338.50(c)(3)(i). One comment stated that incorporation of this warning, based on a recommendation of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, fails to recognize the difference between the dosage and pattern of use of antihistamines in OTC nighttime sleep-aid products and antihistamines in cough/cold products. The comment also cited testimony that a particular sleep-aid drug product containing methapyrilene and scopolamine is safe when administered to patients with glaucoma (Ref. 1).

The agency recognizes that antihistamines used as OTC nighttime sleep-aids are taken only once a day, whereas they may be taken up to six times a day for cough/cold symptoms. However, the nighttime sleep-aid dosage is often higher than the cough/cold dosage. In addition, there is variation between the different antihistamine drugs with respect to the degree of expected side effects, and also marked individual variation in response to antihistamine drugs (Ref. 2). Thus, the agency believes it best to advise consumers with glaucoma to seek the advice of a physician before using antihistamine-containing OTC drug products. The warning, therefore, has been retained in the OTC nighttime sleep-aid final monograph. The comment's cited testimony does not support deleting this warning because neither methapyrilene nor scopolamine

...ment is correct that there is no evidence to show that repeating the OTC nighttime sleep-aid dose would not be safe and effective. ...data on a repeat dose in 4 hours were not submitted to the agency and the comment presented none. In addition, the data that were submitted demonstrated that the antihistamines are an effective sleep-aid after only one dose has been taken. Therefore, the directions for use in this final rule have not been revised to include a repeat dose.

19. One comment recommended that the agency adopt a "Labeling General Statement" in the final monograph to explain FDA's position on the following aspects of OTC drug labeling: Confusing claims, unsupported or misleading claims, claims implying a unique action, statement of quantity of active ingredients, declaration of inactive ingredients, and general warning statements.

The agency believes that the OTC drug regulations in Part 330 explain the agency's policy regarding many of the items outlined by the comment. For example, § 330.1(e) explains the position regarding inactive ingredients in OTC drug products; § 330.1(g) contains general warning statements that should be included on all OTC drug products (see also discussion of the general pregnancy-nursing warning in comment 17 above); § 330.1(j) recommends that he labeling contain the quantitative amounts of active ingredient per dosage unit; and § 330.10(a)(4)(v) states that "labeling shall be clear and truthful in all respects and may not be false or misleading in any particular." Specific labeling claims or problems are adequately discussed in the respective rulemakings. In light of the discussion above, the agency does not believe it is necessary to adopt a general labeling statement as recommended by the comment.

C. Comments on Combination Drug Products

20. One comment disagreed with the agency's conclusions regarding combinations of OTC nighttime sleep-aids with analgesic ingredients. Specifically, the comment objected to the agency's insistence on factorially designed studies to demonstrate a target population that would benefit from such combinations. The comment contended that there is compelling logic for the existence of a target population of individuals with sleeplessness due to pain and that the tension component of pain produces a degree of sleeplessness beyond that produced by the pain itself. Although an analgesic may relieve the pain and indirectly relieve the tension and allow for sleep, the nighttime sleep-aid ingredient will enhance this effect by directly relieving the tension and its resultant sleeplessness. The comment referred to a published article to support this theory (Ref. 1).

The comment further argued that the OTC drug regulations in § 330.10(a)(4)(iv) do not require a showing that each ingredient in a combination product is needed. The comment pointed out that the regulations for prescription drug combination products (21 CFR 300.50) make it mandatory not only that each ingredient make a contribution, "but also that there be a significant patient population requiring such concurrent therapy." The comment stated that the absence of such specific language in the OTC drug regulations makes it clear that, for OTC drug combinations, each ingredient does not have to be shown to be needed.

Several comments submitted results of a number of studies in which nighttime sleep-aid/analgesic combination drug products were evaluated to determine whether such combinations should be generally recognized as safe and effective in the final monograph (Ref. 2). One comment also requested a hearing on this issue.

The article cited by the comment (Ref. 1) does not support the claimed theory that the addition of an antihistamine to an analgesic, for use in individuals with sleeplessness due to pain, provides for relief of the tension component of pain and its resultant sleeplessness. In this randomized, double-blind, crossover study, 206 patients were treated for "simple nervous tension accompanied by headache" using phenyltoloxamine citrate alone, acetaminophen alone, the combination of these two drugs, or placebo. The subjects rated each treatment with respect to degree of relief and time interval until maximum relief was obtained for each of the symptoms of tension, anxiety, irritability, and headache. Sleep was not a measured parameter in this study and, therefore, the study is of little value in assessing the effectiveness of the antihistamine in providing or enhancing a sleep effect.

The agency has also reviewed the clinical studies and information submitted in the other comments (Ref. 2). These studies contain new data on the safety and effectiveness of a combination of two analgesics with diphenhydramine for use as a nighttime pain reliever. These studies, however, "do not provide comparisons between the combinations and their individual antihistamine and analgesic components" (Ref. 3). The agency concludes that the available data remain insufficient to demonstrate whether the addition of a nighttime sleep-aid enhances the effectiveness of the analgesic to allow labeling the product as a "nighttime pain reliever."

Regarding the need to identify a target population that could benefit from an OTC nighttime pain reliever, the agency recognizes the fact that the study design proposed in the OTC nighttime sleep-aid tentative final monograph separated the test population into two groups, i.e., individuals with sleeplessness related to pain and those who suffer from sleeplessness not related to pain. In proposing this latter group, the agency recognized the existence of a suitable target population for the combination of an OTC nighttime sleep-aid and internal analgesic(s). In this patient population are individuals who might on a given night have both sleep problems and mild to moderate pain. In cases where only one symptom occurs, it is more appropriate to select drugs separately for specific symptomatic relief.

Since publication of the Panel's findings and the tentative final monograph, the agency announced on November 28, 1978, the availability of a guideline that states in detail its policy for combining two or more safe and effective OTC active drug ingredients (43 FR 55466). The agency uses this guideline in addition to the existing regulatory requirements for OTC combination drugs in § 330.10(a)(4)(iv). The guideline is currently available for public examination at FDA's Dockets Management Branch (Docket No. 78D-0322). Item (1) of the guidelines states, "Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects."

In reviewing the information available several years ago, the agency tentatively concluded that the combination of an OTC nighttime sleep-aid and OTC internal analgesic(s) was reasonable, provided the combination was properly labeled for use only when concurrent symptoms exist, e.g., for occasional minor aches, pains, and headache with accompanying sleeplessness. Accordingly, at that time, the agency planned to reclassify the combination of a nighttime sleep-aid and internal analgesic(s) from Category III to Category I.

mean sleep latency to first persistent sleep, the objective variable used as a criterion for entrance into the study, increased with pyrilamine by 18 minutes. Thus, the persistent sleep latency actually worsened with pyrilamine as compared to the placebo baseline nights. For the subjective variables, there were no comparisons that were significant at $p=0.05$.

On April 16, 1982, additional information was submitted to the agency (Ref. 5), including letters from Drs. Fabre, Hartmann, and Vogel addressing the agency's comments and evaluation (Ref. 6) on their studies. In a letter dated April 4, 1983, the agency discussed its review of these letters and concluded that the data provide insufficient evidence of effectiveness for pyrilamine as an OTC nighttime sleep-aid (Ref. 7). In its letter, FDA discussed the following:

(1) There were no analyses of the first period data of the Fabre study (Ref. 2) despite the fact that the lack of such analyses was addressed earlier in the agency's comments and evaluation of June 17, 1981 (Ref. 6). The data submitted are still based on analyses which are not appropriate for crossover studies, and there was no satisfactory explanation for the large disparity between the results of the Austin and Houston clinics. It is difficult to conclude that these differences could be attributed to the demographic differences between the two clinics as suggested by Dr. Fabre.

(2) Of the five efficacy variables (sleep latency, number of awakenings, total time spent awake, sleep duration, and sleep quality) suggested for testing in the Hartmann, Marsh, and Soderland study (Ref. 3), none favor pyrilamine at the 0.05 level of significance. Only two variables (sleep latency and quality of sleep) favor pyrilamine and only at the 0.10 significance level (Ref. 8). The agency has reviewed the new analysis by Dr. Hartmann, which reportedly demonstrates the superiority of pyrilamine compared to placebo at greater statistical significance if subjects with a sleep latency in excess of 15 minutes are analyzed separately. It was necessary to exclude slightly more than half of the patients who could be evaluated in order to show a difference in sleep latency that favored pyrilamine at the 0.05 level of significance. Little weight can be attached to results that were obtained by excluding more than half of the patients on the basis of an apparently arbitrary criterion.

Dr. Hartmann has stated that his patients had mild sleep latency problems, but generally were not suffering from other forms of insomnia. The fact that less than half the patients' usual sleep latency exceeded 15 minutes, and only for 13 percent did it exceed 30 minutes, leads to the conclusion that these patients' sleep latency problems were so mild that the inconclusive results may be attributed to poor patient selection.

(3) The results of the Vogel study (Ref. 4) do not show that pyrilamine reduces sleep latency. Based on the fact that sleep laboratory studies have been able to show an effect on sleep latency for two other OTC nighttime sleep-aids (diphenhydramine and doxylamine), the agency concludes that the results of this study do not support pyrilamine's claim of effectiveness as a nighttime sleep-aid.

Based on the additional information submitted, the agency concludes that the data are still inadequate to include pyrilamine in the monograph (Category I) for use as an OTC nighttime sleep-aid. The agency's detailed comments and evaluation of the additional information are on file in the Dockets Management Branch (Refs. 6, 7, and 8).

References

(1) Comment No. C00031, Docket No. 75N-0244, Dockets Management Branch.

(2) Fabre, L.F., "Double-Blind Controlled Evaluation of Pyrilamine Maleate and Placebo in Insomniac Patients Suffering Primarily From Difficulties Falling Asleep," unpublished study No. I, Comment Nos. C00033 and SUP006, Docket No. 75N-0244, Dockets Management Branch.

(3) Hartmann, E.L., E.B. Marsh, and C.A. Soderland, "The Clinical Evaluation of Pyrilamine Maleate vs. Placebo as a Nighttime Sleep-aid for Patients With Occasional Non-chronic Insomnia," unpublished study No. II, Comment Nos. C00033 and SUP006, Docket No. 75N-0244, Dockets Management Branch.

(4) Vogel, G.W., "The Effects of Pyrilamine Maleate 50 mg on the Sleep Cycle of Healthy Adults with Insomnia," unpublished study No. III, Comment Nos. C00033 and SUP006, Docket No. 75N-0244, Dockets Management Branch.

(5) Letter from A.G. Eckian to W.E. Gilbertson, FDA, coded LET008, Docket No. 75N-0244, Dockets Management Branch.

(6) Letter from W. E. Gilbertson, FDA, to A. G. Eckian, coded LET005, Docket No. 75N-0244, Dockets Management Branch.

(7) Letter from W. E. Gilbertson, FDA, to A. G. Eckian, coded LET011, Docket No. 75N-0244, Dockets Management Branch.

(8) Letter from W. E. Gilbertson, FDA, to A. G. Eckian, coded CR0003, Docket No. 75N-0244, Dockets Management Branch.

E. Comments on Diphenhydramine

22. The results of several studies were submitted to support general recognition of the safety and effectiveness of diphenhydramine hydrochloride and diphenhydramine citrate as OTC nighttime sleep-aid ingredients (Refs. 1 through 12). Diphenhydramine hydrochloride was evaluated in eight studies (Refs. 1 through 8) and diphenhydramine citrate in the other four studies (Refs. 9 through 12).

The agency finds that many of the clinical studies conducted with diphenhydramine hydrochloride (Refs. 1 through 8) were conducted on hospitalized patients and not on the target population, e.g., mild insomniacs, or lacked proper sample size or protocol design and therefore are supportive of effectiveness, but do not alone establish general recognition of OTC safety and effectiveness. For example, one double-blind placebo-controlled study (Ref. 5) compared the effects of 50 mg and 100 mg diphenhydramine hydrochloride in 584 post-ophthalmic surgery patients at the Massachusetts Eye and Ear Infirmary who anticipated having trouble sleeping. The duration of therapy was one night. Side effects were also measured and grouped into eight categories. Both the 50 mg and 100 mg doses of diphenhydramine hydrochloride were significantly superior to placebo. The differences in efficacy between the 50 mg and 100 mg doses were not statistically significant although the incidence of anticholinergic side effects was significantly higher in the 100-mg group. The incidence of other side effects was low with no significant differences between the two drug groups and the placebo group. This study is acceptable as evidence of the hypnotic efficacy and safety of diphenhydramine hydrochloride. The study establishes the optimal dose of diphenhydramine hydrochloride as 50 mg because the 100-mg dose was associated with a significant increase in anticholinergic side effects with no added increase in effectiveness.

The studies by Rickels (Ref. 8) and Finnerty and Goldberg (Ref. 7), conducted in Philadelphia and Boston, support the effectiveness of diphenhydramine as a nighttime sleep-aid. These studies were randomized, double-blind, two-treatment, two-period crossover studies with each period lasting 1 week. Both studies compared 50 mg diphenhydramine hydrochloride to placebo in healthy adults who had mild nonchronic insomnia.

In the Philadelphia study, diphenhydramine hydrochloride was significantly better ($p=0.05$) than placebo for sleep latency, degree to which medication helped, depth of sleep, and quality of sleep. At the less conservative 0.10 level of significance, diphenhydramine was better than placebo for the amount of time spent awake in bed.

criminal investigations between 1975 and 1982, but because diphenhydramine is not scheduled in the Controlled Substances Act, it is not a primary object of those criminal investigations in which it is encountered.

The comment noted that data from the Drug Abuse Warning Network (DAWN) compiled by the National Institute on Drug Abuse (NIDA) have ranked diphenhydramine in the "Top 50" list of drugs mentioned in overdose cases seen in hospital emergency rooms and that for the period from January to July of 1981, diphenhydramine ranked 27th on the list, higher than many controlled substances, including methadone, LSD, barbiturates, ethchlorvynol, codeine, meprobamate, meperidine, amphetamine, oxazepam, and hydromorphone (Ref. 2). The comment added that, in 1981, 29 percent (396) of the overdose victims included in the DAWN data used diphenhydramine alone, and the remaining 71 percent (961) used diphenhydramine in various combinations. The comment stated that the motivation for taking diphenhydramine was attributed to psychic effects or dependence in 25 percent, or 333 cases, and suicide attempts in 58 percent, or 781 cases. The comment pointed out that the main source of diphenhydramine for an overdose victim was through legal prescription, but that between 1979 and 1981, a significant and increasing source of the drug was from illicit sources—thefts and "street buys."

The comment urged FDA to consider the STRIDE and DAWN data prior to issuing rules that would make diphenhydramine more available to the drug abuse community, i.e., through OTC marketing. The comment argued that, in addition to STRIDE and DAWN data, the diphenhydramine abuse portrait includes diversion from foreign drug manufacturers, transportation to clandestine laboratories in South America, illicit formulation into methaqualone "look-alikes," smuggling into the United States, and domestic pharmacy theft.

The agency has reviewed the data submitted by the comment and concludes that these data do not present a clear picture of deliberate misuse and abuse of diphenhydramine, nor do they show that diphenhydramine marketed OTC as a nighttime sleep-aid at a recommended dose of 50 mg of diphenhydramine hydrochloride or 78 mg of diphenhydramine monocitrate is likely to become a serious risk to public health through abuse.

The STRIDE data illustrate that diphenhydramine had been used to produce counterfeit methaqualone tablets, but do not show that diphenhydramine was in demand for itself. An illicit international trade in both the commercially manufactured and the clandestinely manufactured counterfeit methaqualone tablets used to exist with a wide geographic distribution. However, FDA has removed methaqualone from the United States market. (See the Federal Register of September 17, 1984; 49 FR 36441.) Therefore, the agency does not believe that the counterfeiting program that previously existed is a sufficient basis to keep diphenhydramine off the OTC market.

An overdose per se does not necessarily mean that the drug in question is a drug of abuse. Certainly, so far as the trafficking and diversion data are concerned, it appears that diphenhydramine was primarily a drug of deceit and only secondarily a drug of abuse. With reference to the listing of diphenhydramine in the DAWN "Top 50" list, the agency questions whether the overdose victims were knowingly taking diphenhydramine or whether they were taking diphenhydramine manufactured to resemble a prescription drug product containing methaqualone and represented to them as methaqualone. A number of OTC drugs have been involved in the illicit look-alike drug market, and the agency is convinced of the seriousness of the situation. However, misuse of a drug such as diphenhydramine that occurs because the drug is represented as a more potent substance does not necessarily mean that the drug itself is a drug of abuse. (See also comment 10 above.)

The agency is concerned about the possibility of any adverse effects resulting from the use of OTC drug products, but it also recognizes that a number of substances in the marketplace have the potential for misuse by some individuals. However, this is not sufficient reason for withholding such drugs from legitimate OTC uses for which they are safe and effective. The reports of diphenhydramine abuse cited by the comment do not indicate a widespread problem, nor do they show any correlation between this abuse and OTC marketing of the drug. Therefore, at this time the agency finds no reason why diphenhydramine should not be available OTC as a nighttime sleep-aid. Nevertheless, the agency will continue to monitor this situation carefully and will take appropriate action if additional information should become available concerning diphenhydramine abuse as a result of OTC marketing.

References

(1) Trafficking Information on Diphenhydramine Retrieved from STRIDE, January 1975 to April 1982, OTC Volume 050FM, Docket No. 75N–0244, Dockets Management Branch.

(2) Top Fifty Estimates of Specific Drug Mentions, OTC Volume 050FM, Docket No. 75N–0244, Dockets Management Branch.

F. Comments on Scopolamine

24. One comment requested the agency to reconsider the Category II classification of scopolamine compounds and reclassify these ingredients in Category III for use in combination with other OTC nighttime sleep-aid ingredients.

The agency's conclusions on scopolamine compounds as nighttime sleep-aid ingredients were previously set forth in the tentative final monograph on OTC nighttime sleep-aid drug products (43 FR 25544 at 25548 and 25575–25578). The comment has provided no reason to alter these conclusions, nor have any new data been submitted to the agency since publication of the tentative final monograph. Therefore, scopolamine compounds will not be included in the OTC nighttime sleep-aid final monograph.

II. Summary of Significant Changes to the Proposed Rule

1. The agency has redesignated proposed Subpart D as Subpart C and has placed the labeling sections of the monograph in Subpart C.

2. The claim "reduces time to fall asleep if you have difficulty falling asleep" has been added to the Indications section of the monograph. The indication "helps fall asleep" has been revised to read "helps you fall asleep if you have difficulty falling asleep." (See comment 12 above.)

3. The definition of a nighttime sleep-aid has been revised slightly. (See comment 12 above.)

4. The warning in § 338.50(c)(3) has been expanded to be consistent with the warning proposed in the tentative final monograph for OTC antihistamine drug products to read "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." (For discussion of the need to expand the warning, see the Federal Register of January 15, 1985; 50 FR 2200 at 2215.) The previously proposed requirement that this warning be in type at least twice the size as other warnings is not

for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 338.3 Definition.

As used in this part:

Nighttime sleep-aid. A drug that is useful for the relief of occasional sleeplessness by individuals who have difficulty falling asleep.

Subpart B—Active Ingredients

§ 338.10 Nighttime sleep-aid active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 338.50(d):

(a) Diphenhydramine hydrochloride.

(b) Diphenhydramine citrate.

Subpart C—Labeling

§ 338.50 Labeling of nighttime sleep-aid drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "nighttime sleep-aid."

(b) *Indications.* The labeling of the product states, under the heading "Indications," one or more of the phrases listed in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) ("Helps you" or "Reduces time to") "fall asleep if you have difficulty falling asleep."

(2) "For relief of occasional sleeplessness."

(3) "Helps to reduce difficulty falling asleep."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) "Do not give to children under 12 years of age."

(2) "If sleeplessness persists continuously for more than 2 weeks, consult your doctor. Insomnia may be a symptom of serious underlying medical illness."

(3) "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(4) "Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing diphenhydramine hydrochloride identified in § 338.10(a).* Adults and children 12 years of age and over: Oral dosage is 50 milligrams at bedtime if needed, or as directed by a doctor.

(2) *For products containing diphenhydramine citrate identified in § 338.10(b).* Adults and children 12 years of age and over: Oral dosage is 76 milligrams at bedtime if needed, or as directed by a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

Dated: January 17, 1989.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 89-3384 Filed 2-13-89; 8:45 am]

BILLING CODE 4160-01-M

FDA agrees that the manufacturer must know how much preservative is contained in the orange juice as purchased. The agency concludes that the percent by weight of the preservative used, regardless of the amount, should be declared on the label as required by the present regulations and has so provided in the final regulation.

5. Two comments opposed the proposed label statement that "this food must be used only for further manufacturing." They asserted that this statement is unnecessary because these foods are generally packed in drums or barels to be used for further manufacturing and could not be sold at retail.

The agency agrees that if these foods are packed in drums or barrels, the proposed label statement is unnecessary. However, because of its concern over the possibility that the products could inadvertently be sold through retail channels if the two foods are packed in containers other than drums or barrels, FDA is requiring that when the foods are packed in containers whose capacities are less than 19 liters (5 gallons), the label shall bear a statement indicating that the foods are "for further manufacturing use only."

6. One comment stated that the proposed provision that would require each of the optional ingredients used to be declared on the label is unnecessary because the only ingredients present are orange juice or concentrated orange juice and preservative. The comment claimed that a statement of the percent by weight and name of the preservative used coupled with the name of the food is a complete list of ingredients, and suggested that any other listing would be redundant.

FDA agrees that if a preservative is the only optional ingredient used in these foods, the declaration of the preservative used along with the name of the food on the principal display panel constitutes a list of the optional ingredients used as required by 21 CFR Part 101. However, if concentrated orange juice with preservative (§ 146.154) contains a sweetener as permitted by the standard, then a listing of all optional ingredients used shall appear together on either the principal display panel or information panel of the label.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 401, 701(e), 52 Stat. 1046 as amended, 70 Stat. 919 as amended (21 U.S.C. 341, 371(e))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Part 146 is amended as follows:

1. In § 146.152 by revising paragraphs (b) and (d) to read as follows:

§ 146.152 Orange juice with preservative.

* * * * *

(b) The preservatives referred to in paragraph (a) of this section are any safe and suitable preservatives or combinations thereof.

* * * * *

(d) Each of the optional ingredients used shall be declared on the label as required by the applicable sections of Part 101 of this chapter. In addition, the name of each preservative shall be preceded by a statement of the percent by weight of the preservative used. If the food is packed in container sizes that are less than 19 liters (5 gallons), the label shall bear a statement indicating that the food is for further manufacturing use only.

* * * * *

2. In § 146.154 by revising paragraphs (b) and (d) to read as follows:

§ 146.154 Concentrated orange juice with preservative.

* * * * *

(b) The preservatives referred to in paragraph (a) of this section are any safe and suitable preservatives or combinations thereof.

* * * * *

(d) Each of the optional ingredients used shall be declared on the label as required by the applicable sections of Part 101 of this chapter. In addition, the name of each preservative shall be preceded by a statement of the percent by weight of the preservative used. If the food is packed in container sizes that are less than 19 liters (5 gallons), the label shall bear a statement indicating that the food is for further manufacturing use only.

* * * * *

Any person who will be adversely affected by the foregoing regulation may at any time on or before July 23, 1979, submit to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, written objections thereto and may make a written request for a public hearing on the stated objections. Each objection shall be separately numbered and each numbered objection shall specify with particularity the provision of the regulation to which objection is made. Each numbered objection on which a hearing is requested shall specifically so state; failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hear is requested shall include a detailed description and analysis of the speci factual information intended to be presented in support of the objection the event that a hearing is held; failu to include such a description and analysis for any particular objection shall constitute a waiver of the right hearing on the objection. Four copies all documents shall be submitted an shall be identified with the Hearing Clerk docket number found in brack in the heading of this regulation. Received objections may be seen in above office between the hours of 9 and 4 p.m., Monday through Friday.

Effective date. Except as to any provisions that may be stayed by the filing of proper objections, complian with this final regulation, including a required labeling changes, may begi July 23, 1979, and all products initiall introduced into interstate commerce or after July 1, 1981 shall fully compl Notice of the filing of objections or l thereof will be published in the Fede Register.

(Secs. 401, 701(e), 52 Stat. 1046 as amend 70 Stat. 919 as amended (21 U.S.C. 341, 371(e)).)

Dated: June 13, 1979.

Joseph P. Hile,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 79-18316 Filed 6-21-79; 8:45 am]

BILLING CODE 4110-03-M

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21 CFR Part 310

[Docket No. 75N–0244]

Drugs for Human Use; Over-the-Counter (OTC) Daytime Sedatives

AGENCY: Food and Drug Administra

ACTION: Final order.

SUMMARY: This document contains t final decision that any ingredient wl labeled for use as an over-the-count (OTC) daytime sedative is not gener recognized as safe and effective for intended use. Any product marketec this use would be subject to regulat action unless it is the subject of an approved new drug application. The Commissioner of Food and Drugs is taking this action after considering public comments on the tentative fir order published in the Federal Regis of June 13, 1978 (43 FR 25544). This f decision is part of FDA's ongoing re of OTC drug products.

EFFECTIVE DATE: December 24, 1979.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: In the Federal Register of December 3, 1975 (40 FR 57292), the agency, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), issued a proposal to establish monographs for OTC nighttime sleep-aid, daytime sedative, and stimulant drug products, together with the conclusions and recommendations of the Advisory Review Panel on OTC Sedative, Sleep-Aid, and Tranquilizer Drug Products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), the data and information considered by the Panel were put on public display in the office of the Hearing Clerk, Food and Drug Administration (FDA), Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, after deletion of trade secret information.

Tentative final orders pertaining to OTC nighttime sleep-aid and stimulant drug products were published in the Federal Register of June 13, 1978 (43 FR 25544). OTC daytime sedatives were discussed in the preamble to those orders but did not appear in a monograph included with the orders because all OTC daytime sedatives were placed in Category II as not generally recognized as safe and effective for OTC use. Interested persons were invited to file, within 30 days, written objections and to request an oral hearing before the Commissioner regarding the tentative final orders.

This order contains the agency's final decision on OTC daytime sedative drug products only. The agency's final decision on OTC nighttime sleep-aid and stimulant drug products will be discussed in future documents. Accordingly, only those comments and portions of comments addressed to the agency's conclusions on daytime sedatives (43 FR 25593) are discussed below. In response to the tentative final order, five comments were received from three consumers, one consumer group, and one manufacturer.

A. The Agency's Conclusions on the Comments

1. Comments from individual consumers expressed personal opinions in favor of or in opposition to the agency's decision to place daytime sedatives in Category II. The comment in favor of the decision stated that taking this action will reduce the number of drugs that are subject to abuse. The comments opposed to the decision stated that certain OTC daytime sedative products had provided relief for particular conditions (sleeplessness and headache) which are unrelated to the indications for a daytime sedative.

The comments opposed to the agency's decision to place OTC daytime sedatives in Category II provided personal testimony in support of specific OTC daytime sedative products but did not offer any reason to change the agency's decision. The agency reaffirms the conclusions stated in paragraph 38 of the preamble to the June 13, 1978 tentative final orders.

2. One comment urged FDA to take action outside the normal regulatory procedures to immediately remove scopolamine from OTC daytime sedative products because scopolamine is both unsafe and ineffective for this intended use.

The agency's policy with respect to ingredients in OTC drug products has been to take action outside the normal OTC regulatory process only when continued marketing of the ingredient poses a sufficient health hazard, e.g., halogenated salicylanilides. The agency stated in paragraph 71 of the preamble to the June 13, 1978 tentative final orders that the available data do not warrant initiating action outside the normal OTC drug review administrative process because the level of scopolamine contained in marketed OTC daytime sedative products is too low to warrant a serious safety concern. The comment provided no reason why the agency should reach a different conclusion at this time. In any case, according to the agency's information, since publication of the December 3, 1975 proposal many manufacturers of OTC daytime sedatives have reformulated their products to eliminate scopolamine. Moreover, publication of the final order contained in this document will require removal of all daytime sedatives, including any which still contain scopolamine, from the OTC market.

3. One comment stated that members of the OTC Sedative, Sleep-Aid, and Tranquilizer Panel were pressured by FDA officials to change, for legal reasons, the Panel's original recommendation that OTC daytime sedatives be placed in Category II. The comment demanded an investigation of such influence by FDA officials to seek full disclosure of those involved.

These same allegations were made in a hearing before the Subcommittee on Monopoly and Anticompetitive Activities of the Select Committee on Small Business, United States Senate, held in Washington, DC, on June 14 and 21, 1977. A copy of the record of those proceedings has been placed on public display in the agency's office of the Hearing Clerk, address given above. At the Senate hearing, one member of the OTC Sedative, Sleep-Aid, and Tranquilizer Panel stated that FDA officials pressured Panel members to "water down" the Panel's Category II recommendations by urging that daytime sedatives be placed in Category III because the available data did not support placing antihistamine products in Category II. This view was contradicted by the Panel Chairman, who wanted "to make it very clear that FDA did not exert any undue influence on the Panel, and certainly not on the Chairman." Another Panel member testified that, while disappointed with the Panel's majority decision to move daytime sedatives from Category II to Category III, the member "did not feel it was due to any undue pressures by the Chairman or the FDA." The agency therefore rejects the position asserted in the comment.

4. One comment requested a hearing to present objections to the agency's proposal to place methapyrilene-containing daytime sedatives in Category II. The comment merely stated "We herewith request a hearing before the Food and Drug Administration in order to present our objections," but did not specify what the objections were.

Section 330.10(a)(7) of the regulations (21 CFR 330.10(a)(7)) states that any objections to a tentative final monograph are to be supported by a brief statement of the grounds for the objections and that a request for an oral hearing may accompany such objections. Section 330.10(a)(8) (21 CFR 330.10(a)(8)) states that the Commissioner will schedule an oral hearing if the grounds in support of the objections are reasonable. Because the person requesting a hearing did not give any statement of the grounds for the objections, and because the agency is unaware of any reasonable grounds that would justify a hearing on the issues relating to daytime sedatives, the hearing request is denied. Further, the agency and the drug industry are currently taking action to remove methapyrilene-containing drug products from the market in response to recent findings by the National Cancer Institute that methapyrilene is a carcinogen. Thus, the request for a hearing would serve no purpose

B. The Agency's Final Conclusions on OTC Daytime Sedative Drug Products

Antihistamines, bromides, and scopolamine compounds, either singly or in combination with other ingredients, e.g., analgesics, amino acids, and vitamins, have been marketed for use as OTC daytime sedatives (or similar or related indications). The following claims were submitted for the daytime sedative products: "occasional simple nervous tension," "nervous irritability," "nervous headache," "simple nervousness due to common every day overwork and fatigue," "a relaxed feeling," "calming down and relaxing," "gently soothe away the tension," "calmative," and "resolving that irritability that ruins your day." The agency is also aware of the following claims that have been associated with these drugs: "helps you relax," "restlessness," "when you're under occasional stress . . . helps you work relaxed."

While antihistamine drugs, when used as daytime sedatives, make the user drowsy or sleepy, there are no data to indicate that the drowsiness effect is related to relieving symptoms of anxiety. Drowsiness is in fact an undesirable side effect for persons using these products during the day, when they need to be alert. Accordingly, the agency concludes that antihistamines should be classified in Category II because they are not generally recognized as safe or effective when used as daytime sedatives.

The bromide compounds are being placed in Category II because they do not act as daytime sedatives in a single dose and, if taken over a long enough period of time to reach therapeutic levels, could be severely toxic.

The scopolamine compounds are classified in Category II because they are ineffective at presently marketed doses. At higher doses that would achieve a therapeutic effect (drowsiness), the scopolamine compounds are unsafe because of the potential for toxic effects associated with these doses. In addition, as stated in the paragraph discussing antihistamines, drowsiness is unrelated to the desired therapeutic effect of daytime sedative products.

The agency is unaware of any OTC daytime sedative drug product that is the subject of an approved new drug application.

Based on the available evidence, the agency is making a final determination that no ingredient can be generally recognized as safe and effective for use as an OTC daytime sedative. If the labeling of any product represents or suggests it to be used as an OTC daytime sedative (or any similar or related indication) that product will be considered a new drug within the meaning of section 201 (p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) and may not be marketed for this use unless it is the subject of an approved new drug application.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended (21 U.S.C. 321(p), 352, 355, 371)) and the Administrative Procedure Act (5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to the Commissioner (21 CFR 5.1), Subchapter D of Title 21 of the Code of Federal Regulations is amended by adding new § 310.519 to read as follows:

§ 310.519 Drug products marketed as over-the-counter (OTC) daytime sedatives.

(a) Antihistamines, bromides, and scopolamine compounds, either singly or in combinations, have been marketed as ingredients in over-the-counter (OTC) drug products for use as daytime sedatives. The following claims have been made for daytime sedative products: "occasional simple nervous tension," "nervous irritability," "nervous headache," "simple nervousness due to common every day overwork and fatigue," "a relaxed feeling," "calming down and relaxing," "gently soothe away the tension," "calmative," "resolving that irritability that ruins your day," "helps you relax," "restlessness," "when you're under occasional stress . . . helps you work relaxed." Based on evidence presently available, there are no ingredients that can be generally recognized as safe and effective for use as OTC daytime sedatives.

(b) Any OTC drug product that is labeled, represented, or promoted as an OTC daytime sedative (or any similar or related indication) is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that such a preparation is safe for the purpose intended.

(d) Any OTC daytime sedative drug product introduced into interstate commerce after December 24, 1979, that is not in compliance with this section is subject to regulatory action.

Effective date. This order will be effective December 24, 1979.

(Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended 1050–1053 as amended, 1055–1056 as amended (21 U.S.C. 321(p), 352, 355, 371) (5 U.S.C. 553, 554, 702, 703, 704).)

Dated: June 18, 1979.

Sherwin Gardner,

Acting Commissioner of Food and Drugs.

[FR Doc. 79-19446 Filed 6-21-79; 8:45 am]

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21 CFR Part 520

Oral Dosage Form New Animal Drugs Not Subject to Certification; Pyrantel Pamoate Suspension

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The animal drug regulations are amended to reflect approval of a supplemental new animal drug application (NADA) filed by Pfizer, Inc., providing for safe and effective use of a higher concentration of a currently approved anthelmintic suspension for removal of roundworms and hookworms in dogs.

EFFECTIVE DATE: June 22, 1979.

FOR FURTHER INFORMATION CONTACT: Bob G. Griffith, Bureau of Veterinary Medicine (HFV–112), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3420.

SUPPLEMENTARY INFORMATION: Pfizer, Inc., 235 E. 42d St., New York, NY 10017, filed a supplemental NADA providing for use of a suspension of 4.54 milligrams of pyrantel (as pyrantel pamoate) per milliliter for removal of roundworms and hookworms in dogs. Pfizer currently holds approval for a suspension containing 2.27 milligrams of pyrantel base per milliliter. This supplemental dosage form covers only a change in concentration of active ingredient from 2.27 milligrams per milliliter to 4.54 milligrams per milliliter. No change is being made in the approved conditions of use, and no added risk of toxicity is present from the inadvertent overdosage of this new concentration. Therefore, under the Bureau's supplemental policy, the approval of this supplemental application has not required a reevaluation of the parent NADA.

In accordance with the freedom of information regulations and § 514.11(e)(2)(ii) of the animal drug